



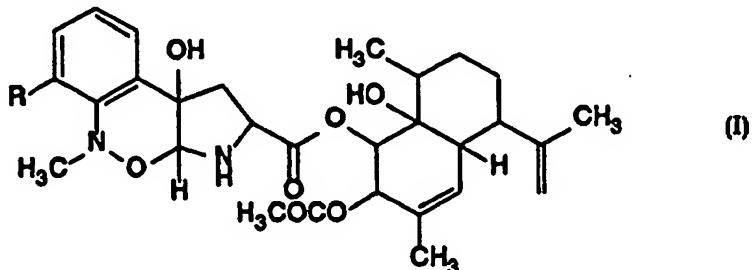
INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 498/04, C12P 17/18, A61K 31/535 // (C07D 498/04, 265:00, 209:00) (C12P 17/18, C12R 1:66)		A1	(11) International Publication Number: WO 95/19363 (43) International Publication Date: 20 July 1995 (20.07.95)
(21) International Application Number: PCT/JP95/00025			(74) Agent: KOBAYASHI, Hiroshi; Pfizer Pharmaceuticals Inc., Shinjuku Mitsui Building, 1-1, Nishi-shinjuku 2-chome, Shinjuku-ku, Tokyo 163-04 (JP).
(22) International Filing Date: 11 January 1995 (11.01.95)			(81) Designated States: AU, CA, JP, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).
(30) Priority Data: 6/15825 14 January 1994 (14.01.94) JP			Published With international search report.
(71) Applicant (for all designated States except JP US): PFIZER INC. [US/US]; 235 East 42nd Street, New York, NY 10017-5755 (US).			
(71) Applicant (for JP only): PFIZER PHARMACEUTICALS INC. [JP/JP]; Shinjuku Mitsui Building, 1-1, Nishi-shinjuku 2-chome, Shinjuku-ku, Tokyo 163-04 (JP).			
(72) Inventors; and			
(75) Inventors/Applicants (for US only): KOJIMA, Yasuhiro [JP/JP]; 83-2, Kaminawa, Heisaka-cho, Nishio-shi, Aichi-ken 444-03 (JP). YAMAUCHI, Yuji [JP/JP]; 1-98-3, Itayama-cho, Handa-shi, Aichi-ken 475 (JP). KOJIMA, Nakao [JP/JP]; 3-153-1, Yashirodai, Meito-ku, Nagoya-shi, Aichi-ken 465 (JP). BISHOP, Bernard, F. [GB/GB]; 5 Liss Road, Eastry, Nr. Sandwich, Kent (GB).			

(54) Title: ANTIPARASITIC PYRROLOBENZOXAZINE COMPOUNDS

(57) Abstract

This invention provides compounds of chemical formula (I) or their pharmaceutically acceptable salts, wherein R is hydrogen or chloro. Also, the present invention provides a process for the production of the compound of formula (I), which comprises cultivating a microorganism having the identifying characteristics of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618 or the like, and then isolating the compound of formula (I) from the fermentation broth. The pyrrolobenzoxazine compounds of formula (I) of this invention have broad antiparasitic activity, and thus are useful as antiparasitic agents, especially as anthelmintics.



FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

ANTIPARASITIC PYRROLOBENZOXAZINE COMPOUNDSTechnical Field

5 The present invention relates to novel pyrrolobenzoxazine compounds, a process for their production and their use. More particularly, the present invention relates to a process for production of novel pyrrolobenzoxazine compounds by cultivating *Aspergillus fischeri* var. *thermomutatus* ATCC 18618. Further, the present invention relates to an antiparasitic agent which comprises a
10 pyrrolobenzoxazine compound of this invention as an effective ingredient.

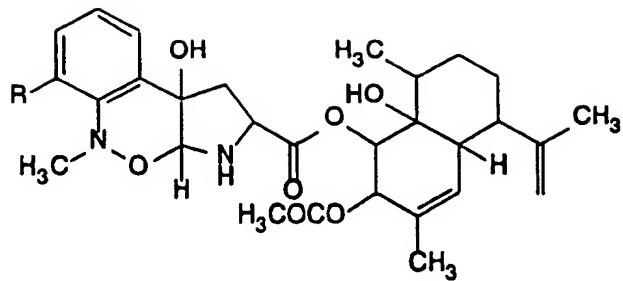
Background Art

It is known that the pyrrolobenzoxazine UK-88,051 is a broad spectrum antiparasitic agent possessing anthelmintic, ectoparasiticidal, insecticidal activity with application in the areas of animal and human health, agriculture and horticulture
15 (United Kingdom Patent No. 2240100). This compound is produced by fermentation of a fungal microorganism *Chrysosporium* sp. ATCC 20975. In this field, the investigation on novel compounds having excellent activity has been continuously carried out.

An objective of the present invention is to provide novel compounds with
20 excellent activity against insect pests, acari, helminths (e.g., free living nematodes) and endo- and ecto-parasites afflicting animals. Also, another objective of the present invention is to provide a process for producing such compounds, and a pharmaceutical composition comprising the same.

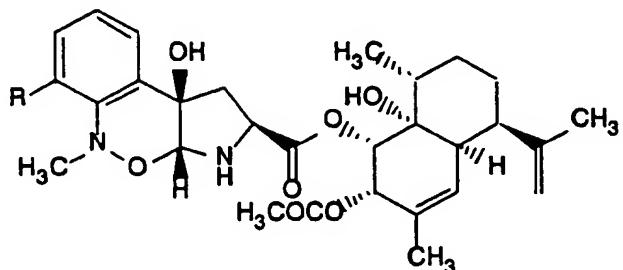
Brief Disclosure of the Invention

25 Accordingly, the present invention provides novel pyrrolobenzoxazine compounds of the following planar chemical formula or their pharmaceutically-acceptable salts:



(I)

wherein R is hydrogen or chloro. It is believed that these compounds have the following absolute chemical formula:



(A)

wherein R is hydrogen or chloro.

Also, the present invention provides a process for the production of the compound of formula I, which comprises fermenting a microorganism having the identifying characteristics of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, or a mutant, genetically-transformed or recombinant form thereof, having the ability to produce the compound of formula I, and then isolating the compound of formula I from the fermentation broth.

The pyrrolobenzoxazine compounds of formula I of this invention have broad antiparasitic activity, and thus are useful as antiparasitic agents, especially as ectoparasiticides. Accordingly, the present invention also provides a pharmaceutical composition for the treatment or prevention of parasitic infection in mammalian

subject which comprises a therapeutically-effective amount of the compound of formula I together with a pharmaceutically-acceptable carrier; and a method for the treatment or prevention of a parasitic infection in non-human mammalian subject, which comprises administering to said subject a therapeutically-effective amount of
5 the compound of formula I.

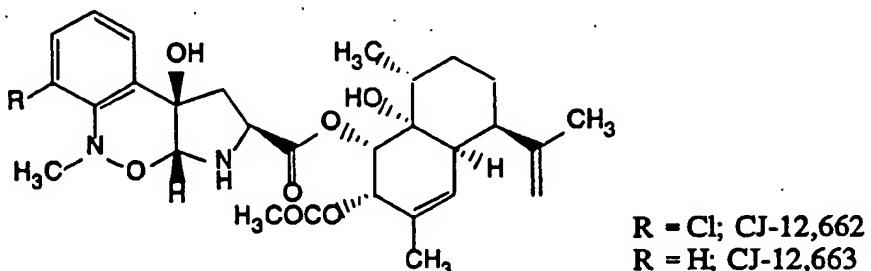
Detailed Description of the Invention

The culture which produces the compounds of the present invention, *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, was obtained from the American Type Culture Collection (ATCC located in 12301 Parklawn Drive, 10 Rockville, Maryland 20852, USA). The taxonomical properties of *A. fischeri* var. *thermomutatus* ATCC 18618 are reported in the literature (Mycopathol. Mycol. Appl., 36, 161-164, 1968). The culture has been deposited further at Agency of Industrial Science and Technology located in 1-3, Higashi 1-chome Tsukuba-shi, Ibaraki-ken, Japan on December 15, 1993, under Accession No. FERM BP-4497.

15 In addition, mutant strains of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, can be used. Such mutant strains can be obtained spontaneously, or by the application of known techniques, such as exposure to ionising radiation, ultraviolet light, and/or chemical mutagens such as N-methyl-N-nitrosourethane, N-methyl-N'-nitro-N-nitrosoguanidine, ethyl methyl sulphate, etc. Genetically transformed and 20 recombinant forms include mutants and genetic variants produced by genetic engineering techniques, including for example recombination, transformation, transduction, protoplast fusion, etc. The invention also extends to pyrrolobenzoxazine compounds produced by said process.

25 Fermentation of the culture ATCC 18618 can be carried out using standard procedures, well-known in the art for fungi of the genus *Aspergillus*. For example, fermentation may take place on suitable solid media under aerobic conditions at a temperature in the range of 20 to 45 °C for 3 to 30 days, preferably at 24 to 37 °C for 7 to 21 days. Alternatively, fermentation may take place in aqueous nutrient media containing suitable sources of carbon, nitrogen and trace elements such as iron, 30 cobalt, copper and zinc for a period of several days under aerobic conditions at a temperature in the range at 20 to 45 °C for 2 to 21 days, preferably at 24 to 37 °C for 3 to 10 days.

The novel pyrrolobenzoxazine compounds of the present invention, 2-acetoxy-1,2,4a,5,6,7,8,8a-octahydro-8a-hydroxy-3,8-dimethyl-5-(1-methylethenyl)-1-naphthalenyl 6-chloro-1,2,3,3a,5,9b-hexahydro-9b-hydroxy-5-methylpyrrolo[2,3-c][2,1]benzoxazine-2-carboxylate (CJ-12,662) and 2-acetoxy-1,2,4a,5,6,7,8,8a-octahydro-8a-hydroxy-3,8-dimethyl-5-(1-methylethenyl)-1-naphthalenyl 2,3,3a,5,9b-hexahydro-9b-hydroxy-5-methylpyrrolo[2,3-c][2,1]benzoxazine-2-carboxylate (CJ-12,663), which are shown in the following scheme, are obtained from fermentation of the culture ATCC 18618, and can be separated by conventional extractions and various techniques of chromatography.



10

Though the novel pyrrolobenzoxazine compounds of this invention are slightly soluble in water, they are easily soluble in organic solvents. Thus, the novel pyrrolobenzoxazine compounds can be recovered from the fermentation broth by solvent extraction. For example, the whole fermentation broth is partitioned between water and an organic solvent such as chloroform, ethyl acetate or methyl isobutyl ketone. The extract is dried over drying agent and concentrated. The residue dissolved in adequate solvent is chromatographed to separate the pyrrolobenzoxazine compounds by eluting with a solvent (a single solvent or mixture of the solvents with various ratios, such as hexane : EtOAc = 1 : 1). Many kinds of powder solids such as silica gel, reverse phase silica gel or dextran can be used as supports or stationary phases. High performance liquid chromatography (HPLC) and thin layer chromatography (TLC) are advantageous for separating the pyrrolobenzoxazine compounds. The existence of the pyrrolobenzoxazine compounds can be confirmed by measuring the antiparasitic activity for each fraction of the chromatography.

The acid addition salts of a compound of formula I of this invention are prepared by treating carefully the present compound with a substantially equivalent amount of the chosen mineral or organic acid in an aqueous solvent or in a suitable organic solvent. Upon careful evaporation of the solvent, the desired solid salt is readily obtained. The acids which are used to prepare the pharmaceutically-acceptable acid addition salts of the aforementioned pyrrolobenzoxazine base compounds of this invention are those which form non-toxic acid addition salts, i.e., salts containing pharmaceutically-acceptable anions such as hydrochloride, hydrobromide, hydroiodide, nitrate, sulfate or bisulfate, phosphate or acid phosphate, acetate, lactate, citrate or acid citrate, tartrate or bi-tartrate, succinate, maleate, fumarate, gluconate, saccharate, benzoate, methanesulfonate, ethanesulfonate, benzenesulfonate, p-toluenesulfonate and pamoate. The antiparasitic activity of the compounds of formula I against the larval stage of the blowfly Lucilia cuprina is measured by using a standard procedure (e.g., Techniques for testing Insecticides, Ed. J. R. Busvine Publ. Commonwealth Institute for Entomology London, 1957) in which first instar larvae are kept in contact with filter paper treated with a test compound. The test compound is first applied to the paper as an acetone solution. The treated filter papers are then placed in tubes containing foetal calf serum and the first instars are added. CJ-12,662 killed 100 % of the larvae when applied to the filter paper at a level of 40 mg/m².

The pyrrolobenzoxazine compounds of formula I of this invention are useful as antiparasitic agents in a variety of mammalian species including man.

They can be used for the prevention or treatment of systemic infections caused by endoparasites including, in particular, helminthiasis which is most frequently caused by a group of parasitic worms described as nematodes and which can cause severe economic losses in mammals such as swine, sheep, horses and cattle as well as affecting domestic animals and poultry. They are also of value in treating ectoparasite infections including in particular arthropod ectoparasites of animals and birds such as ticks, mites, lice fleas, blowfly, biting insects and migrating dipetrous larvae which affect cattle and horses. They are also insecticides, active against household pests such as the cockroach, clothes moth, carpet beetle and the housefly as well as being useful against insect pests of stored grain and of agricultural plants

such as spider mites, aphids, caterpillars and against migratory orthopterans such as locusts.

For these purposes, they can be administered to a mammalian subject orally or parenterally.

5 As an alternative, the compounds of formula I may be administered with the animal feedstuff and for this purpose a concentrated feed additive or premix may be prepared for mixing with the normal animal feed.

The novel pyrrolobenzoxazine compounds of the present invention may be administered alone or in combination with pharmaceutically-acceptable carriers or diluents, and such administration can be carried out in single or multiple doses. 10 Particularly, the novel therapeutic agents of the invention can be administered in a wide variety of different dosage forms, i.e., they may be combined with various pharmaceutically-acceptable inert carriers in the form of tablets, capsules, lozenges, troches, hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, 15 pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups and the like. For use as an insecticide and for treating agricultural pests, sprays, dusts, pour-on formulations, emulsions and the like are preferable in accordance with standard veterinary practice. Such carriers include solid diluents or fillers, sterile aqueous media, various non-toxic organic solvents, etc. Moreover, oral 20 pharmaceutical compositions can be suitably sweetened and/or flavored. In general, the therapeutically-effective compounds of this invention are present in such dosage forms at concentration levels ranging about 5 to 70% by weight.

For oral administration, tablets containing various excipients such as microcrystalline cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, the addition of lubricating agents such as magnesium stearate, sodium lauryl sulfate and talc is often very useful for tabletting purposes. Solid 25 compositions of a similar type may also be employed as fillers in gelatine capsules: preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs 30

are desired for oral administration, the active ingredient may be combined with various sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.

5 For parenteral administration, solutions of the pyrrolobenzoxazine compounds of the present invention in either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous solutions should be suitably buffered (preferably pH > 8) if necessary, and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes. The oily solutions are
10 suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily accomplished by standard pharmaceutical techniques well-known to those skilled in the art.

15 Additionally, it is also possible to administer the compounds of the present invention topically to an affected part such as the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments, pour-ons, sprays and the like, in accordance with standard pharmaceutical practice.

20 The formulations will vary with regard to the weight of active compound, depending on the species of host mammalian to be treated, and depending on the severity and type of infection and the body weight of the host. Generally a dosage level that is in the range of from about 1 to 100 mg per kg of body weight per day is desirably employed. Nevertheless, when administering to the animals, variations may still occur depending upon the species of animal being treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out.
25 In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful side effects provided that such higher dose levels are first divided into several small doses for administration throughout the day.

EXAMPLES

30 The present invention is illustrated by the following example. However, it should be understood that the invention is not limited to the specific details of this example. UV spectra were recorded using a Hewlett Packard 1090M diode-array

spectrophotometer. All NMR spectra were measured in CDCl_3 by a Varian Unity 500MHz spectrometer unless otherwise indicated and peak positions are expressed in parts per million (ppm) downfield from tetramethylsilane. The peak shapes are denoted as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, 5 broad. Mass spectra (LSIMS) were measured by a Kratos Concept 1S mass spectrometer. Thermospray mass spectrometry was performed using a VG-Trio-1000 quadrupole mass spectrometer. Samples were introduced from methanolic solution directly on the probe.

Example 1

10 The culture *Aspergillus fischeri* var. *thermomutatus* ATCC 18618 was inoculated on a slant of ATCC Medium 325 consisting of malt extract 20 g, glucose 20 g, peptone 1 g, agar 20 g and distilled water 1 l, and incubated at 26°C for 2 weeks. Spore suspension of the mature slant culture was used to inoculate a solid production medium in a 1-l Erlenmyer flask. The solid production medium in the 15 flask consisted of glucose 0.5 g, glycerol 1.5 g, peptone 0.25 g, NaCl 0.1 g, bran 20 g and tap water 50 ml. Thirty solid production flasks were incubated under stationary conditions at 26°C for 2 weeks. Two hundred ml of acetone was added to each of the 30 1-l flasks; contents of these flasks were then combined, stirred and filtered. After removal of the solvent, the residue was extracted with 2 l of ethyl 20 acetate. The extract was dried over anhydrous Na_2SO_4 and evaporated. The resultant oily residue (3 g) was loaded on a silica gel column (Merck Kieselgel 60, 70-230 mesh) and eluted with *n*-hexane : ethyl acetate (1 : 1). Then further purification was carried out on a Sephadex LH-20 column (3.0 x 90 cm, MeOH). Fractions with antiparasitic activity were combined and concentrated. The active 25 fraction was applied to preparative HPLC (YMC-Pack ODS-AM column 5 μ , methanol : H_2O = 4 : 1) to obtain pure CJ-12,662 (129 mg) and CJ-12,663 (27 mg).

Physico-chemical properties of CJ-12,662

Formula: $\text{C}_{29}\text{H}_{37}\text{N}_2\text{O}_7\text{Cl}$
30 LSIMS m/z = 561.239 ($\text{M}+\text{H})^+$ (Calcd.: 561.245 for $\text{C}_{29}\text{H}_{37}\text{N}_2\text{O}_7\text{Cl}$)
UV λ nm: 217, 248, 287

5 ¹H NMR (CDCl₃): 7.4 (1H, d), 7.25 (1H, d), 7.05 (1H, t), 5.5 (1H, bs), 5.4 (1H, bs), 5.2 (2H, m), 5.05 (1H, bs), 4.8 (1H, bs), 4.15 (1H, m), 3.65 (1H, bs), 3.35 (3H, s), 3.1 (1H, s), 2.75 (1H, m), 2.5-2.65 (3H, m), 2.35 (1H, s), 2.15 (3H, s), 2.0-2.15 (1H, m), 1.85 (3H, s), 1.65 (3H, s), 1.3-1.65 (4H, m) and 0.9 (3H, d).

10 ¹³C NMR (CDCl₃): 174.9 (s), 169.9 (s), 146.5 (s), 144.1 (s), 131.6 (s), 129.9 (d), 129.6 (s), 127.3 (d), 125.7 (d), 124.4 (d), 123.5 (s), 111.5 (t), 84.5 (d), 76.1 (s), 74.3 (d), 73.4 (s), 72.7 (d), 58.2 (d), 42.1 (q), 41.2 (t), 40.9 (d), 39.2 (d), 30.6 (d), 30.1 (t), 25.8 (t), 22.4 (q), 20.7 (q), 19.7 (q) and 14.6 (q).

Physico-chemical properties of CJ-12,663

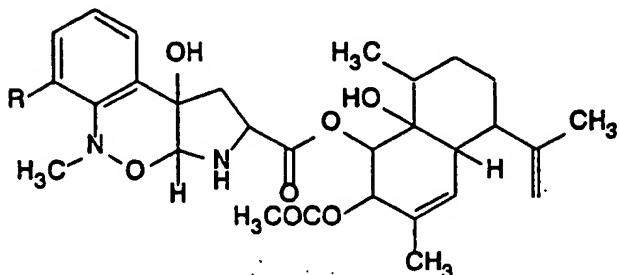
15 Formula: C₂₉H₃₈N₂O₇

UV λ nm: 217, 248, 287

16 Mass spectrum (thermospray) m/z = 527 (M+H)⁺
(Calcd.: 527 for C₂₉H₃₈N₂O₇·H⁺)
17 ¹H NMR (CDCl₃): 7.45 (1H, d), 7.25 (1H, dd), 7.0 (1H, dd), 6.75 (d, 1H), 5.5 (1H, bs), 5.4 (1H, bs), 5.2 (2H, m), 5.05 (1H, bs), 4.8 (1H, bs), 4.15 (1H, d), 4.0 (1H, m), 3.2 (3H, s), 2.45-2.9 (6H, m), 2.25 (3H, s), 1.9-2.2 (1H, m), 1.9 (3H, s), 1.7 (3H, s), 1.3-1.65 (4H, m) and 0.9 (3H, d).

CLAIMS

1. A compound of formula (I) or its pharmaceutically- acceptable salts:



5

(I)

wherein R is hydrogen or chloro.

10

2. A compound according to claim 1, wherein R is hydrogen.

3. A compound according to claim 1, wherein R is chloro.

15

4. A process for the production of a compound according to claim 1, which comprises cultivating a microorganism having the identifying characteristics of *Aspergillus fischeri* var. *thermomutatus* ATCC 18618, or a mutant, genetically-transformed or recombinant form thereof, having the ability to produce a compound according to claim 1, and then isolating a compound of claim 1 from the fermentation broth.

15

5. A process according to claim 4, wherein the cultivation is carried out under aerobic conditions on a nutrient solid medium or in a nutrient aqueous medium containing assimilable sources of carbon, nitrogen and minerals, until a significant amount of a compound of claim 1 accumulates.

20

6. A process according to claim 5, wherein the microorganism is *Aspergillus fischeri* var. *thermomutatus* ATCC 18618.

7. A pharmaceutical composition for the treatment or prevention of parasitic infection in mammalian subject, which comprises a therapeutically-

effective amount of a compound according to claim 1 together with a pharmaceutically-acceptable carrier.

5

8. A pharmaceutical composition according to claim 7 in the form of an oral, injectable or pour-on formulation, or in the form of a spray or dust, or in the form of a concentrated feed additive, premix or supplement for incorporation with the normal animal feed.

10

9. A method for the treatment or prevention of a parasitic infection in non-human mammalian subject, which comprises administering to said subject a therapeutically-effective amount of a compound according to claim 1.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/JP 95/00025

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D498/04 C12P17/18 A61K31/535 // (C07D498/04, 265:00,
209:00), (C12P17/18, C12R1:66)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07D C12P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB,A,2 240 100 (PFIZER) 24 July 1991 cited in the application see claims 1,3 -----	1,7

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *I* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

& document member of the same patent family

1

Date of the actual completion of the international search

23 March 1995

Date of mailing of the international search report

31.03.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Fax. 31 651 cpo nl.
Fax (+31-70) 340-3016

Authorized officer

Voyiazoglou, D

INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP 95/00025

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 9 is directed to a method of treatment of (diagnostic method practised on) the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

The additional search fees were accompanied by the applicant's protest

No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/JP 95/00025

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
GB-A-2240100	24-07-91	NONE	